UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/310,685	05/04/1999	JONATHAN ROBERT LAMB	674525-2001	9186

20999 7590 12/02/2002

FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
DECLOUX, AMY M	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/02/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/310,685	LAMB ET AL.	
	Examiner	Art Unit	
	Amy M. DeCloux	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-25,32 and 40-47* is/are pending in the application.

4a) Of the above claim(s) *7-25,32,40 and 41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-44 and 47* is/are rejected.

7)☒ Claim(s) *45 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and declarations filed 8-22-02 (Paper No. 23) are acknowledged and have been entered.

In view of Applicant's amendment all outstanding rejections have been withdrawn. However, a new ground of rejection has been applied to newly added claims 42-47.

It is noted that Applicant submitted claims numbered 42-44 and 46-48. Claims 46-48 have been renumbered as claims 45-47, respectively, under Rule 1.126

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

A) Claims 42-44 and 47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 42-44 and 47 are drawn to a method of reducing T cell activation by administering a notch ligand comprising a DSL domain to a patient in need thereof.

The instant specification discloses on pages 10-12, that the notch ligands are preferably delta or serrate family members proteins or polypeptides or derivatives thereof, and include fragments thereof and derivatives of such fragments, and also includes the protein product of Delta, Serrate, as well as other members of this gene family identifiable by virtue of their gene sequences that hybridize to, or have homology with Notch Delta or Serrate proteins, or the ability of their genes to display phenotypic interactions.

However, the instant specification does not describe a method of reducing T cell activation comprising administering a notch ligand, except for the notch ligands of full length delta and full length serrate. Applicant's declarations filed 8-22-02 (Paper No. 23) state that fragments of delta and serrate that contain the DSL element are also effective in said method. However, the instant specification does not describe the recited method comprising administering a notch ligand other than delta or serrate.

In view of the disclosed broad definition of notch ligand that encompasses any of a number of known and unknown notch ligands, and in view of Artavanis-Tsakonas et al's teaching that Notch is a multifunctional receptor, (Science (1995) Vol 268:225-232, see entire

article, especially the first sentence of page 229), there is insufficient written description in the instant specification to allow one of skill in the art to distinguish between the genus of notch ligands that interact with notch and reduce T cell activation, compared to the genus of notch ligands which may not reduce T cell activation.

Without a description of the structural basis for the biological interaction of T cells with notch ligands, known and unknown, it is not clear how one would visualize a notch ligand (except for full length delta or full length serrate, or a fragment of delta or serrate containing the DSL element) which could be administered in a method of reducing T cell activation.

Without a further description of the structural basis for the interaction of the T cells with a notch ligand, one of ordinary skill could not establish the boundaries of the genus of a notch ligand based only on the disclosure of full length Serrate and Delta, wherein said genus would be administered in a method of reducing T cell activation as claimed instantly. It is noted that though the claimed invention is directed to polypeptides and not cDNA, the principle of the following still holds for said polypeptides: a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.)

Therefore, only a method of reducing T cell activation comprising administering the notch ligands consisting of full length Serrate and Delta, or a fragment of delta or serrate containing the DSL element, but not the full breadth of the instant claims, meets the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

B) Claims 42-44 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing T cell activity comprising administering a notch ligand comprising a DSL domain wherein said notch ligand is delta or serrate, does not reasonably provide enablement for said method comprising administering any notch ligand comprising a DSL domain . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention without an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858iF2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the level of predictability in the art, the state of the prior art, the amount of experimentation required to make or use the invention based on the content of the disclosure, the amount of guidance and direction presented, and the existence of working examples.

The instant claims are drawn to a method of reducing T cell activity comprising administering a notch ligand comprising a DSL domain.

However, the specification does not enable one of skill in the art regarding a method of reducing T cell activity comprising administering any notch ligand comprising a DSL domain.

The instant specification discloses on page 3 and Example 1 shows that notch, delta and serrate are expressed in the peripheral immune system of the mouse, Serrate being expressed on a subpopulation of antigen presenting cells and Delta's being expressed in a subset of T cells, though it is not clear from the instant disclosure what those subsets are. The instant specification also discloses in Example 4 and 10 shows that primed lymph node cells show reduced antigen specific proliferation when stimulated by irradiated T cell hybridomas transfected with full length Delta than T cell hybridomas transfected with vector alone, and also discloses in example 6 that lymph node cells from mice injected with said hybridomas and immunized with allergen showed reduced proliferation and Il-2 secretion 7 days later in vitro when incubated with said allergen. Example 5 shows that naive mice immunized with HDDM-peptide-pulsed dendritic cells (Dcs) transfected with full length Serrate, produce 10 fold fewer recoverable LN cells, and that mice immunized with DCs and full length Serrate produce Lymph node cells that fail to proliferate or secrete IL-2. Similar results were disclosed using T cell clone reactive with an influenza peptide in examples 7 and 8. The instant specification also discloses in examples 11 and 12 that Delta is expressed on T cells during the induction of tolerance.

However, though these examples demonstrate a suppressive effect of full length serrate and full length Delta on T cell activation, it is not clear from the instant disclosure how these results enable one of skill to practice a method of reducing T cell activity comprising administering any notch ligand comprising a DSL domain as recited in the instant claims, (other than serrate and delta), since the instant specification provides insufficient guidance and direction regarding the effectiveness of any notch ligand other than Serrate or Delta in reducing T cell activity. This guidance is especially needed in view of the unclear nature of which notch receptors and which notch ligands are expressed on which lymphoid cells (such as antigen presenting cells, NK cells, T cell subsets and/or which other immune cells), as evidenced by the instant specification's disclosure on page 3 that the expression pattern of the notch family of receptors and their ligands in the normal peripheral adult immune system has not been previously described, and by Jaleco et al.'s teaching (Meeting Abstract (2001) Blood 98 (11): Part 2, page 117b) that the notch ligands delta and jagged can mediate differential effects of Notch signaling on B cells, T/NK cells, and CD4+/CD8+ cells, and by Janeway's teaching (Immunobiology,

Fourth Edition, Garland Press, 1999, page 246) that notch protein overexpressed in thymocytes directs them to the CD8 lineage and may inhibit the pathway to CD4 T cells. In re Fisher, 1666 USPQ 19 24 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the disclosed broad definition of notch ligand that encompasses any of a number of known and unknown notch ligands, and in view of Artavanis-Tsakonas et al's teaching that Notch is a multifunctional receptor, (Science (1995) Vol 268:225-232, see entire article, especially the first sentence of page 229), there is insufficient guidance and direction in the instant specification to allow one of skill in the art to predict which notch ligands interact with notch and reduce T cell activation, and to predict those that don't. Without a description of the structural basis for the biological interaction of T cells with notch ligands, known and unknown, there is insufficient guidance and direction in the instant specification to allow one of skill in the art to predict which fragment or derivative of a notch ligand such as Serrate or Delta, could be administered in a method of treating T-cell mediated disease or infection, especially in view of Ish-Horowicz et al.'s teachings (U.S. Patent 6,004,924)(1999) that derivatives, including but not limited to fragments and analogs, of serrate proteins can be either inhibitory or can retain one or more of the functions of full length wild type Serrate Protein (see entire patent, especially Section 5.6 in columns 19-20), and the disclosure on page 13 of the instant specification that analogs can be either agonistic or antagonistic of a notch protein or notch ligand.

Therefore it would require undue experimentation for one of skill in the art to predict the efficacy of the administration of any notch ligand comprising a DSL element (with the exception of delta and serrate) in a method of reducing T cell activation, in view of the insufficient guidance and direction regarding the effect of administration any notch ligand. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Allowable Subject Matter

Claims 45 and 46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

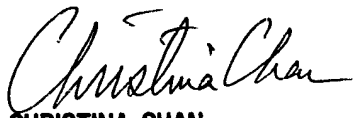
the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305-3014 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, Ph.D.
Patent Examiner, 1644
November 26, 2002



CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600